



## 저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:



저작자표시. 귀하는 원저작자를 표시하여야 합니다.



비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.



변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 [이용허락규약\(Legal Code\)](#)을 이해하기 쉽게 요약한 것입니다.

[Disclaimer](#)

# Mathematical modeling and computation of dengue fever caused by climate change in Jeju Island

Junyeong Lee

Department of Mathematical Sciences

Graduate School of UNIST

2015

# Mathematical modeling and computation of dengue fever caused by climate change in Jeju Island

**Junyeong Lee**

Department of Mathematical Sciences

Graduate School of UNIST

# Mathematical modeling and computation of dengue fever caused by climate change in Jeju Island

A thesis/dissertation  
submitted to the Graduate School of UNIST  
in partial fulfillment of the  
requirements for the degree of  
Doctor of Philosophy/Master of Science

Junyeong Lee

06. 17. 2015

Approved by

A handwritten signature in black ink, appearing to read 'CHANG', is written over a solid horizontal line.

Advisor

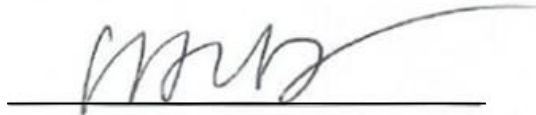
Chang Hyeong Lee

# Mathematical modeling and computation of dengue fever caused by climate change in Jeju Island

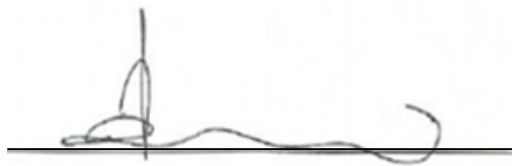
Junyeong Lee

This certifies that the thesis/dissertation of Junyeong Lee is approved.

06. 17. 2015



Advisor: Chang Hyeong Lee



Pilwon Kim: Thesis Committee Member #1



Hae-Sang Sun: Thesis Committee Member #2

## Abstract

Dengue fever which is a vector-borne infectious disease that spreads rapidly in subtropical or tropical countries is rarely recognized as a public health concern in South Korea, especially Jeju Island which is target district for study. However, there is a high possibility that the outbreak of dengue fever occurs in Korea within a few years since global warming is accelerating and the medium mosquitoes for dengue are also inhabit in Korea. The purpose of this study is predicting how many patients would occur when there is an outbreak of dengue fever by using climate change scenario. Based on RCPs provided by Korea Meteorological Administration, the parameters related to mosquitoes represented as fitting functions and specific function by using climatic factors such as temperature, precipitation, and relative humidity are formulated. The simulation for deterministic models is performed by using two methods, one of applying climate data of all the four seasons, and the other applying climate data of seasons excluding winter. This study show the relation between climate change and outbreaks of dengue, which could be an important indicator to establish polices to reduce spread of the disease.



## Contents

I . Introduction -----	1
1.1 Background of research -----	1
1.2 Research objectives -----	2
1.3 Existing research -----	3
II. Mathematical models for epidemic -----	4
2.1 The SIR epidemic model -----	4
2.2 The basic vector-host model -----	6
III. Application: Epidemic models for dengue fever caused by global warming in Jeju Island -----	7
3.1 Research material -----	7
3.2 Research methodology -----	9
3.3 Mathematical models for dengue fever -----	10
3.3.1 Primary infection model -----	11
3.3.2 Secondary infection model -----	12
3.3.3 Two strains model -----	15
3.4 Parameters -----	16
3.5 Results and analysis -----	23
IV. Discussion and Future work -----	30
V. Conclusion -----	33
VI. References -----	35



## List of Figures

**Figure 2.1** Diagram of SIR model

**Figure 2.2** Diagram of basic vector-host model

**Figure 3.1** Difference of two types of temperature based on RCPs

**Figure 3.2** Average of temperature for 50years

**Figure 3.3** Diagram of primary infection model for Dengue Fever

**Figure 3.4** Diagram of secondary infection model with four serotypes

**Figure 3.5** Modified temperature dependent parameters

**Figure 3.6** Five climatic factors dependent parameters related to mosquito for one year

**Figure 3.7** Results for secondary infection model with four serotypes

**Figure 3.8** Results for secondary infection model with two strains

**Figure 3.9** Results for secondary infection model with four serotypes during summer

**Figure 3.10** Results for change of total mosquitoes

**Figure 3.11** Results for spread of infected mosquitoes

**Figure 3.12** Results for spread of primary infectee

**Figure 3.13** Results for spread of secondary infectee

**Figure 3.14** Results for occurrence for the dead

**Figure 4.1** Solutions for deterministic and stochastic primary infection model

**Figure 4.2** Probability of extinction for SIR model

## List of Tables

**Table 3.1** Characteristic of RCP scenarios

**Table 3.2** Specific major serotypes by country

**Table 3.3** Parameters of dengue fever models

**Table 3.4** Modified functions for temperature dependent parameters

**Table 4.1** Difference of two types of solutions

## I . Introduction

### 1.1. Background of Research

Recently, Korea is experiencing huge damages it had never before in the ecosystems, agriculture, health and other areas due to global warming. According to the Trewartha method, if the average temperature of the coldest month is  $18^{\circ}\text{C}$  and there are from 8 to 12 months wherein the monthly average temperature is  $10^{\circ}\text{C}$  or higher, it is defined to be a subtropical climate [1]. Applying this method, Jeju Island and the southern coast area of our country is already classified under the subtropical climate. Analyzing the data on Korea's climate during the 20<sup>th</sup> century based on the data of Korea Meteorological Administration, the average temperature has increased by  $1.5^{\circ}\text{C}$  over the past 100 years; this is a result exceeding the worldwide trend of global warming. Furthermore, it could be predicted that the average temperature of the entire Korean peninsula will increase by  $4^{\circ}\text{C}$  and the average amount of rainfall of the Southern area of Korea will increase by 17% [24]. One of the harmful phenomena recently faced by the ecosystem and consequently affecting health is the spread of insect-borne diseases occurred especially in the subtropical and tropical climates of Korea. The one receiving the most attention among the mosquito-borne diseases is dengue fever. Dengue fever is an acute recessive disease that proliferates through the dengue virus, a type of flavivirus. The symptoms of which are headache, muscle ache, vomiting, and arthralgia. It is rare to die due to the dengue fever among adults. However, if the infection happens consecutively, it could result to dengue hemorrhagic fever or dengue shock syndrome, and in serious cases, sudden hemorrhage or shock can happen during the recovery and then lead to death. The dengue virus has four serotypes. For the type of dengue virus that has already been infected, a life-long immunity is acquired; however, one does not become immune for the other types. For example, if a person contracted the dengue fever due to DEN1, in the following times, he/she may be infected due to DEN2-4, the other serotypes, and may experience dengue hemorrhagic fever or dengue shock syndrome which may have severe symptoms due to consecutive infection [2]. However, there is no special treatment and vaccine for this disease. It is the *Aedes aegypti* and the *Aedes albopictus* of the *Aedes* species that carry these dengue viruses. The *Aedes albopictus* which are spread out in all areas in the Korea is seen as the main culprit in the break out of the dengue fever. Until now, there is no case where a dengue fever occurred in the country; however the number of patients infected with dengue fever from overseas who enter the country has been increasing steadily which implies that Korea is no longer safe from the dengue fever [3]. Mosquitoes are greatly affected by the climate conditions; particularly, temperature, humidity, and the amount of rainfall. If the temperature rises, the

number of entities increases. They actively move and the rate of development from a larva into an imago increases as well. On the one hand, when the temperature is low, the activity significantly decreases or stops. Likewise if the humidity level is high, the number of reproduction of mosquitoes increases as well as their duration of life. Therefore, if the average temperature and comparative humidity generally increase due to global warming, the active period or the duration of life of mosquitoes will be longer than before, increasing the number of mosquitoes and the consequent number of contact with humans. Therefore, the sudden spread of the dengue fever caused by climate change in Korea has been a concern.

## 1.2. Research Objectives

Today, due to active international interactions and worldwide climate change, the inhabitation environment of men and animals have become relatively similar, and due to this, diseases that did not exist in the past are occurring and may spread in a faster speed. For instance, dengue fever hit France and Croatia in the year 2010 and caused a fatality in Greece in 2010 [25]. In 2014, a dengue fever patient was also reported in Tokyo, Japan after 70 years. However, despite the big issues that this causes, there is still a dearth of researches on infectious diseases due to climate change that have been done in the country. Likewise, there still are no exact data on subtropical and tropical diseases which have not yet occurred that fits the reality of Korea. Therefore, the moment these diseases spread, it can cause more confusion than any other disease. As a result, in this point of time, when the possibility of the occurrence and naturalization of new infectious disease annually increase, it is more needed to accurately predict the dispersion process of the infectious disease that may occur in the future through mathematical models made out of various scenarios. Based on the results of these predictions, the government can search and implement corresponding policies in a more accurate manner. In this research, Jeju Island was the chosen region as the subject of the study because it is one region that may get the subtropical infectious disease. Based on the scenario about the climate change in Jeju Island, the dengue fever, the most dangerous disease next to malaria, will be chosen as the subject of the mathematical models to be established. The number of patients and fatalities to occur in the future will be predicted by year, and the change process will be looked into through a simulation. Through this research, the mathematical model of a Korean dengue fever will be established, and a predicting program will be made to enable the government to make more accurate and faster predictions when the disease occurs. The predicted results and the real data will both be used to build a Korean database. Additionally, when new infectious diseases come, the level of riskiness and the corresponding precautionary and preparatory actions will be made to minimize the economic and social costs.

### 1.3. Existing Research

Many countries are using mathematic models of infectious diseases to predict their spread, Representative mathematic models of infectious diseases include the SI model, the SIR model, the SIS model, and the SEIR model according to the characteristics of the diseases and these models are said to be compartment models that show the conditions of the patients by the groups. The SIR model, one of the major models, was devised by Kermack, a Scottish mathematician and Mckendrick, a preventative epidemiologist in 1972 [5], and by using this, they predicted the spread of infectious diseases. This model classifies the entire population into the following 3 groups according to their conditions, and shows how the infectious diseases are spread among the groups: Group S who have no immunity and thus are likely to be infected with the diseases; Group who have been infected with the diseases; and Group I who have acquired immunity after recovering from the diseases. The time-wise function between the groups can be indicated with a differential equation. The equation assumes that people are evenly distributed among all the groups, causing the same probability of the infection caused by their mutual contact, and that the size of the group is fixed since death and birth are constant. Afterwards, the SEIR model was proposed as a way of expanding this model by adding Group E who has been infected with the diseases, but no symptom has been expressed. So far, there have been many studies on infectious diseases performed based on these compartment models [4].

The vector-host model is usually used in order to express mathematically the infection caused by the contact between people and mosquitoes (Adams and Boots, 2010) [7]. Kun (2013) studied the model for the secondary infection with dengue fever virus in reference to the ADE factor [9], while M Derouich (2003) studied the effects of the two different dengue fever viruses on the spread of dengue fever in reference to the bloodsucking ratios of the infected and the uninfected mosquitoes [11]. Furthermore, there are various studies being performed on the effects of the climatic factors (e.g., temperature, relative humidity, etc.) on the spread of dengue fever. Yang (2009) built the model that expressed the effects of the temperature on the spread of dengue fever by estimating the parameters based on the results of his mosquito experiment [10]. Szu (2012) used the temperature data of Kaohsiung City, Taiwan, predicting what specific temperature would cause dengue fever to spread more widely compared to other temperatures [8].

## II. Mathematical Models for epidemic

The mathematical model about communicable diseases is used by various countries as a needed tool for building up national policy in preparation for the spreading of diseases. In addition, using a mathematical model is emphasized because verification through an experiment is impossible and unethical for it deals with a disease. Typically, mathematical model is composed of deterministic model and stochastic model. Mathematical epidemiology uses models based on difference equation, differential equation, and integral equation in order to express the spread of an infection. These kind of models are called deterministic models. In the case of deterministic model, the process of the proliferation of disease is determined due to the parameter values and particular initial condition. In case of deterministic model, one of the most basic infectious disease model, the compartment model, which divides the total population into specific groups and represents transition from one group to other group mathematically as a differential equation is commonly used. However, there are some assumptions in the deterministic model. The possibility that an individual who is part of a group will move to another group is all equal, therefore the differences of an individual's chances to be infected and the differences in his or her immune reaction cannot be considered; and since this model follows the law of mass action, then if the size of a group is big, the speed of movement from that group to another group is high. It is therefore useful when the size of the human group is relatively big. The deterministic model is divided into SIS, SIR, SEIR model according to the characteristics of various diseases and these are the basic models in the compartment model of infection epidemiology. Using these models, there are several advantages. They can provide relatively simple explanation of epidemic process, a solution can be easily calculated. However, they cannot express the characteristics of the individual's in the group especially the random characteristics about stochastic behavior.

### 2.1. The SIR Epidemic Model

Deterministic mathematical model is used when one treats diseases which have affected a large number of the population such as tuberculosis and flu. The widely used one, SIR model, was developed by Kermack and McKendrick in 1927 in order to describe how a disease spread in limited population [5]. Under the assumption that the whole population is fixed well and not changed due to birth, death and migration, this model divided the limited population into three compartments. The following diagram which is **Figure2.1** expresses these compartment and compartment flow which represent transition from one group to other group.



Figure 2.1 Diagram of SIR model

The meaning of each compartment in diagram is as follows:

- Susceptible: Uninfected one, yet open to the possibility of getting diseases due to low level of immunity.
- Infected: Infected one thus has the potential to spread the disease.
- Recovered: Recovered one with high level of immunity. He or she does not spread the diseases even though there's contact with other person.

People move the compartment with the sequence  $S \rightarrow I \rightarrow R$  as inter-epidemic happens with time and called a compartment flow. Mathematically, each compartment can be expressed depending on the size of the time from the time. Differentiation equation, which applies derivatives about time, is used. The number of people in each of the compartments about a differential coefficient of each compartment's size is assumed as the function which can be differentiated. This is appropriate when the compartment's size is big. Moreover, there should be an assumption that the process of spread is deterministic. Expressing the SIR model in a differential equation is as follows:

$$N = S(t) + I(t) + R(t)$$

$$\frac{dS}{dt} = -\beta SI \quad (2.1) \quad \text{where } \beta: \text{transmission rate, } \gamma: \text{recovery rate}$$

$$\frac{dI}{dt} = \beta SI - \gamma I \quad (2.2)$$

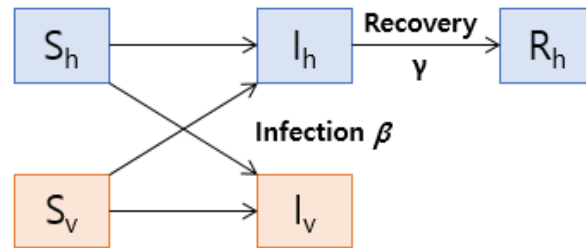
$$\frac{dR}{dt} = \gamma I \quad (2.3)$$

In the first equation,  $\beta SI$  is the new number of infected people made by the contact between the uninfected and the infected one in unit per hour using the ratio of contact or ratio of infection  $\beta$ . Moreover, it also tells us that the population moves from  $S$  compartment to  $I$  compartment. Likewise,

through the recovery rate  $\gamma$ , one will notice that the population moves from  $I$  compartment to  $R$  compartment in the second and the third equations.

## 2.2. The Basic Vector-Host Model

The vector-host model is commonly used expressing vector borne disease such as dengue fever and malaria which are not transmitted directly from host to host, but through a vector. The basic and simple vector-host model was developed by Ross-MacDonald in 1957. The characteristic of this model is representing relation between vector and host by splitting into vector part and host part and coupling a simple SI model for the vectors with SIR model for the hosts shown in **Fig.2.2**.



**Figure 2.2 Diagram of basic vector host model**

Under the assumption that the whole populations of vector and host are well mixed (homogeneous) and not changed due to birth, death and migration, this model divided the limited population into two groups for vector and three groups for host, respectively. In an SI model for vector, the vector population is divided into two groups: Susceptible and Infectious. On the other hands, the host population is divided into three groups in an SIR model for host: Susceptible, Infectious, and Recovered. Susceptible host. This model is based on the following assumptions. First, the size of total mosquito ( $N_v$ ) and human ( $N_h$ ) population are constant. Second, the recovered larva and mosquito are not considered since the life span of mosquito is relatively short and they die under infected condition. In addition, if susceptible host is bitten by infected mosquito or susceptible mosquito bites infected mosquito, the disease can be transmitted randomly. These assumptions translate in the following formulation.



$$\frac{dS_v}{dt} = -\beta \frac{I_h}{N_h} S_v \quad (2.5)$$

$$\frac{dI_v}{dt} = \beta \frac{I_h}{N_h} S_v \quad (2.6)$$

$$\frac{dS_h}{dt} = -\beta \frac{I_v}{N_h} S_h \quad (2.7) \quad \text{where } \beta: \text{transmission rate, } \gamma: \text{recovery rate}$$

$$\frac{dI_h}{dt} = \beta \frac{I_v}{N_h} S_h - \gamma I_h \quad (2.8)$$

$$\frac{dR_h}{dt} = \gamma I_h \quad (2.9)$$

Susceptible host becomes infectious host at a rate  $\beta S_h I_v$  through contact with infected vector. In the same way, susceptible vector becomes infected vector at a rate  $\beta S_v I_h$  by contact with infected host. The parameter  $\gamma$  is the recovery rate for infected host. This basic model can be extended by other form considering pre-adult mosquito or adding other compartment in SIR model for host.

### III. Application

#### : Epidemic models for dengue fever caused by global warming in Jeju Island

##### 3.1. Research Material

###### 3.1.1. Study area

Jeju Island located on the southern coast of South Korea(126°09'N to 127°00'N, 33°10'E to 34°35'E) is selected as a study area. It is the largest province among those of South Korea with a relatively high humid subtropical climate than that of the rest of Korea with distinct four seasons. Due to feature of this climate, the temperature hardly falls below 0°C even in winter and precipitation is quite heavy per year. It is known that the high temperature and humidity can have great effect on development of inhabited environment for mosquitoes. In fact, the habitats of Dengue Fever- carrying mosquito, *Aedes albopictus*, reported being on the increase in this area. Besides, the influx of mosquitoes or tourist infected by Dengue Fever can occur anytime through plane and vessel since there are international airport and several seaports in this area connected with nations in East Asia. For these reasons, this area is worth researching for outbreak and transmission of Dengue Fever for the first time in Korea.

### 3.1.2. Scenario of Climate Change and Climate Data

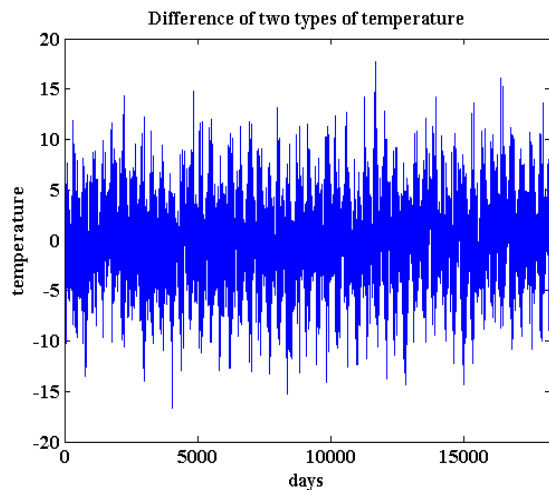
The up-to-the-minute scenario of climate change chosen by Intergovernmental Panel on Climate Change (IPCC) for its fifth Assessment Report (AR5) is RCPs which are characterized by the radiative forcing that is a measure of the energy absorbed and retained in the lower atmosphere. Since they are developed to be representative of possible future emission and concentrate on the concentration of greenhouse gas along with pathway over time to reach a specific radiative forcing, they are called Representative Concentration Pathways.

The RCPs are divided into one mitigation scenario (RCP 2.6), two medium stabilization scenarios (RCP 4.5, RCP 6.0) and one high emission scenario (RCP 8.5). Each of the RCPs is prescribed according to the concentration of carbon dioxide and other greenhouse gas such as carbon monoxide and methane gas. The numbers in each RCP represent to the amount of radiative forcing at the end of 21<sup>st</sup> century. This following table describes each characteristic of RCPs [32].

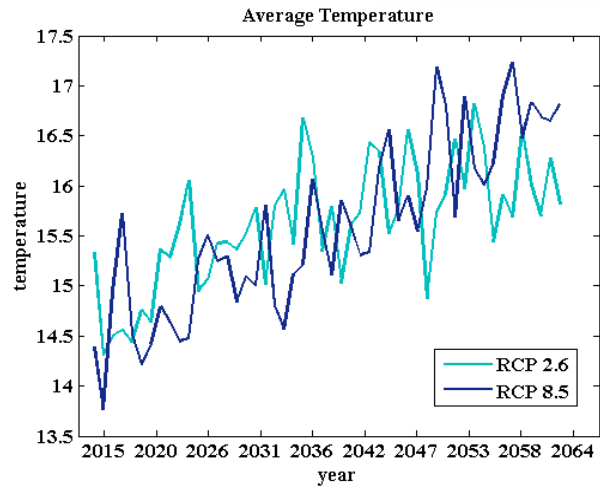
	<b>Radiative Forcing</b>	<b>Concentration of CO<sub>2</sub>(ppm)</b>	<b>Average of Increasing Temperature to 2081-2100 relative to a 1850-1900</b>
RCP 2.6	~3 W/m <sup>2</sup> before 2100, declining to 2.6 W/m <sup>2</sup> by 2100	420 ppm	1.6°C [0.9°C-2.3°C]
RCP 4.5	4.5 W/m <sup>2</sup> after 2100	540 ppm	2.4°C [1.7°C-3.2°C]
RCP 6.0	6.0 W/m <sup>2</sup> after 2100	670 ppm	2.8°C [2.0°C-3.7°C]
RCP 8.5	8.5 W/m <sup>2</sup> in 2100	940 ppm	4.3°C [3.2°C-5.4°C]

**Table 3.1 Characteristic of RCP scenarios**

In this study, the daily data of average temperature, relative humidity, evaporation, precipitation, and dew point in Jeju Island based on RCP 8.5 are used to express the several parameters affecting mosquitoes such as egg laying rate, death rate, virus incubation rate and maturation rate in the fitted functions. By the way, these data are provided by Climate Change Information Center at Korea Meteorological Administration (KMA). The RCP 8.5 is selected in order to obtain the large impact on outbreak of disease. The **Figure 3.1 and 3.2** show the difference of temperature data and average temperature based on RCP 2.6 and 8.5 for 50years.



**Figure 3.1 Difference of two types of temperature**



**Figure 3.2 Average of temperature for 50years**

According to above results, the difference of two mean values of temperature is about  $0.5^{\circ}\text{C}$ , and it is easy to find that the temperature based on RCP 8.5 is relatively higher than that based on RCP 2.6. Although other things do not appear on above graphs such as the highest and lowest temperature, the highest temperatures are  $30.98^{\circ}\text{C}$  and  $30.23^{\circ}\text{C}$ , the lowest temperatures are  $-3.41^{\circ}\text{C}$  and  $-3.21^{\circ}\text{C}$  corresponding to RCP 8.5 and RCP 2.6, respectively.

### 3.2. Research methodology

Since the carriers of the dengue fever are mosquitoes, it is an infectious disease that is more affected by the changes in climate than any other diseases. Thus, in building the mathematical model, climate conditions such as the temperature, relative humidity, and the amount of rainfall that affect the mosquitoes should be considered. Hence, in this research, the climate change scenario which was recently presented by the IPCC – the RCP scenario – was used as a basis. The climate data of the subject, Jeju Island, was applied to come up with a mathematical model. Additionally, it was taken into consideration that infection occurs not in human to human contact, but only with mosquitoes as the entity, and that there are four serotypes of the dengue virus. Though one becomes immune to the serotype once infected, one is still not immune to the others, therefore, making consecutive infections possible that may cause fatalities due to the occurrence of dengue hemorrhagic fever or dengue shock syndrome which have relatively high lethality, and the point that ordinarily, consecutive infection does not occur after the second infection.

In this research, the phenomenon of the contagion of the dengue fever was shown through the first and second infection model. In the cases of mosquitoes, the SI model was used to express the first and second infection in the larval stage and the SEI model for the imagoes. For the cases of humans, the SIR model was used for the first infection and the SIRIR model for the second infection to express the contagion among humans. The parameters regarding mosquitoes were expressed through using fitting functions for particular functions to apply the daily climate data. When making the simulations, two types of the mathematical model were ran assuming that the first occurrence of the dengue fever is January 1, 2014 as the initial condition. The computations and results of the two models and two types of methods were compared and analyzed to predict the month with the highest number of patients, the approximate highest number of patients, and the approximate number of fatalities.

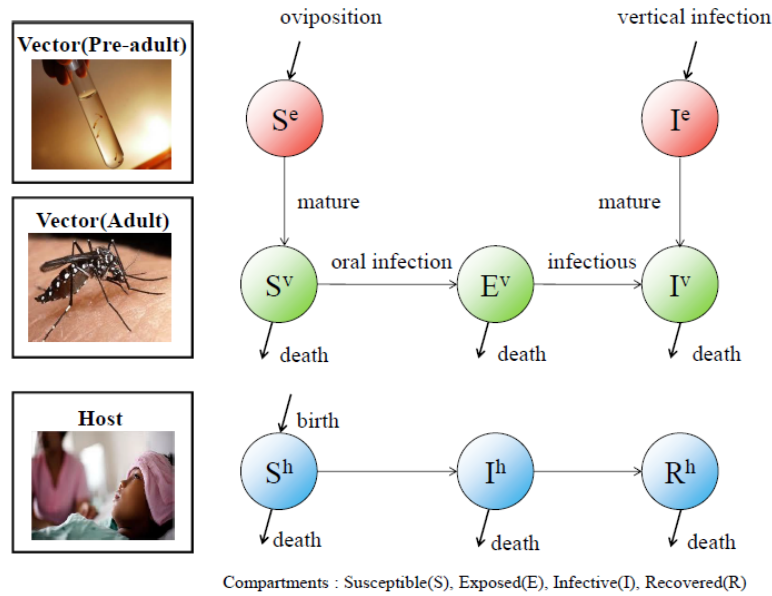
### 3.3. Mathematical Models for Dengue Fever

When population size is sufficiently large, using deterministic models which assume that the current states determine the behavior of the future states is often appropriate. The deterministic model treats the time evolution for a continuous reactions or processes which can be represented by a set of ordinary differential equation. In this model, same initial conditions give the same outputs and no randomness is contained. Since population size in Jeju Island as district of this study is relatively large, it is sufficient to use deterministic model in order to describe the dynamics of dengue fever.

This study adopts the vector-host model for describing dynamics of dengue fever in Jeju Island. In order to formulate the models for this disease, it is mandatory to confirming several characteristics of this contagious disease. Dengue fever is caused by four kinds of serotypes, DEN1, 2, 3 and 4, of a mosquito-borne flavivirus. Although those infected from one serotype cannot be re-infected by that one, they can be infected others. For example, a man infected by DEN1 can be re-infected by not this serotype but one of from DEN2 to DEN4. The sequential infections make patients have greater risk and feel big pain for dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). This phenomenon is called Antibody-Dependent Enhancement. Moreover, when a medium mosquito bites a person infected with dengue fever, the mosquito can be infected. In addition, this disease cannot spread from person to person or from mosquito to mosquito directly. For these characteristics of this disease, it is reasonable to consider all serotypes and processes of infection as important factors to build models.

### 3.3.1. Primary infection model

In this primary infection model [8], it is assumed that the three types of population, human, pre-adult mosquito and adult female mosquito, are taken into account and the specific one of the serotypes plays significant role as key factor which affects spread of this disease. Since considering only one serotype allows only primary infection to occur due to production of antibody for that serotype. The diagram of this model is shown in **Fig 3.3**.



**Figure 3.3 Diagram of primary infection model for Dengue Fever**

Two compartments of pre-adult female mosquito population are defined by susceptible ( $S^e$ ) and infected ( $I^e$ ). In pre-adult mosquito population, three compartments are also defined by susceptible ( $S^v$ ), exposed ( $E^v$ ), and infected ( $I^v$ ). On the other hands, Three compartments of human population are defined by susceptible ( $S^h$ ), infected ( $I^h$ ), and recovered ( $R^h$ ). For instance,  $S^e$  means the number of susceptible pre-adult mosquitoes at time  $t$ . Since the infected mosquito can have no immune once it is infected by some disease, there is no compartment related to its recovering such as  $R^e$  and  $R^v$ .

The eight ordinary differential equations describe this system. The parameters related to mosquito population, egg laying rate  $b_v$ , vertical infection from adult mosquito to pre-adult mosquito  $v$ , maturation rate  $\omega$ , death rate  $\mu_v$ , and virus incubation rate  $\varepsilon$  are described in the equations from (3.1) to (3.5).

$$\frac{dS^e}{dt} = b_v \left( 1 - v \frac{I^v}{N^v} \right) - \omega S^e \quad (3.1)$$

$$\frac{dI^e}{dt} = b_v v \frac{I^v}{N^v} - \omega I^e \quad (3.2)$$

$$\frac{dS^v}{dt} = \omega S^e - \beta \frac{I^h}{N^h} S^v - \mu_v S^v \quad (3.3)$$

$$\frac{dE^v}{dt} = \beta \frac{I^h}{N^h} S^v - \varepsilon E^v - \mu_v E^v \quad (3.4)$$

$$\frac{dI^v}{dt} = \varepsilon E^v + \omega I^e - \mu_v I^v \quad (3.5)$$

$$\frac{dS^h}{dt} = \mu_{hb} N^h - \beta \frac{S^h}{N^h} I^v - \mu_{hd} S^h \quad (3.6)$$

$$\frac{dI^h}{dt} = \beta \frac{S^h}{N^h} I^v - \gamma I^h - \mu_{hd} I^h \quad (3.7)$$

$$\frac{dR^h}{dt} = \gamma I^h - \mu_{hd} R^h \quad (3.8)$$

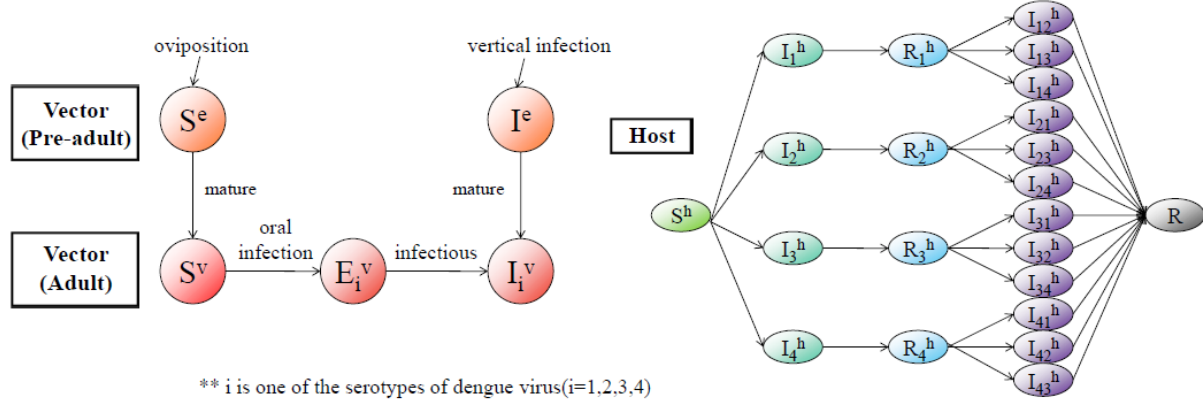
The parameters  $\mu_{hb}$  and  $\mu_{hd}$  represent the human birth rate and death rate, respectively. The parameter  $\beta$  is transmission biting rate obtained by assumption that mosquito bites human once a three days. The parameter  $\gamma$  is recovery rate for human. Define  $S^v + E^v + I^v$  be  $N^v$  as total size of mosquito population and  $S^h + I^h + R^h$  be  $N^h$  as total size of human population. The terms  $I^v/N^v$  and  $I^h/N^h$  represent infection rate in mosquito and human, respectively. The number of population in each compartment can increase or decrease due to migration or immigration such as infection, recovery, birth, and death. For example,  $S^v$  decreases by the term  $\beta(I^h/N^h)S^v$  related to infection from infected human to susceptible mosquito and increases by the term  $\omega S^e$  related to maturation from susceptible pre-adult mosquito to susceptible adult mosquito.

### 3.3.2. Secondary infection model

When dealing with secondary infection for dengue fever, it is essential to consider that the sequentially re-infected patient with a second serotype has larger pain and risk due to DHF and DSS. This comes from the effect of ADE factor. Thus, formulating the secondary infection model is necessary to deal with the dynamics of dengue fever in more detail. Compare with primary infection model, the secondary

infection model contains more compartments as to secondary infection that are  $I_i^h$ ,  $I_{ij}^h$ ,  $R_i^h$ , and  $R$ . Furthermore, the Antibody Dependent Enhancement (ADE) factor  $\phi$  where the existing antibodies to primary infection cannot neutralize but rather enhance the secondary infection by other distinct serotypes is also included in this model. When  $\phi > 1$ , there is an enhancement of secondary infection with respect to primary infection but a reduction occurs when  $\phi < 1$ . In other words, when  $\phi$  is larger than 1, infected individuals in secondary infection can transmit the disease more than those infected primarily.

The full diagram for this model is shown in **Fig 3.4**. The notation of  $i$  means one of the four serotypes (DEN1-DEN4). The mosquito population is divided into susceptible ( $S^v$ ), latent by specific one serotype ( $E_i^v$ ), and infectious with serotype  $i$  ( $I_i^v$ ) for  $i = 1, 2, 3$  and 4. There is no compartment as for recovered individual because infection with specific one serotype gives lifelong immunity to that one. The human population is divided into susceptible ( $S^h$ ), primary infected ( $I_i^h$ ), secondary infected ( $I_{ij}^h$ ) who is the recovered from serotype  $i$  and currently infected by other distinct serotypes  $j$ , and recovered ( $R_i^h$ ,  $R$ ). The thirty three ordinary differential equations represent this system.



**Figure 3.4 Diagram of secondary infection model with four serotypes**

This model involves other three parameters related to mosquito which are not included in the primary infection model such as the rate of infected mosquito bites  $b_i$ , the rate of susceptible mosquito bites  $b_s$ , and the number of mosquito per host  $m$ . Generally, it is known that the infection make the mosquito bite more than usual, therefore, it is assumed that  $b_i$  is greater than  $b_s$ . On the other hand, the two parameters which are not contained in the primary infection model,  $\gamma^h$  and  $\sigma^h$ , are first recovery rate and second recovery rate, respectively. Define  $S^h + I_i^h + R_i^h + I_{ij}^h + R$  be  $N^h$  as the total size of

human. Noting  $\beta^{hv}$  the first transmission rate of an infected human to susceptible mosquito and also  $\beta^{vh}$  the first transmission rate of an infected mosquito to susceptible human, the rates of first exposure to this disease for mosquito and human are  $b_s m \beta^{hv} I_i^h / N^h$  and  $b_i m \beta^{vh} I_i^v / N^h$ , respectively. Furthermore, the rates of sequentially secondary exposure for mosquito and human are represented by the terms in the differential equations as  $\phi b_s m \beta^{hv} I_{ji}^h / N^h$  and  $\phi b_i m \beta^{vh} I_i^v / N^h$ , respectively.

**<Vector>**

$$\frac{dS^e}{dt} = b_v \left( 1 - \sum_{i=1}^4 v \frac{I_i^v}{N^v} \right) - \omega S^e \quad (3.9)$$

$$\frac{dI_i^e}{dt} = b_v v \frac{I_i^v}{N^v} - \omega I_i^e \quad (3.10)$$

$$\frac{dS^v}{dt} = \omega S^e - S^v \left( \sum_{i=1, i \neq j}^4 b_s m \beta^{hv} \frac{I_i^h + \phi I_{ji}^h}{N^h} \right) - \mu_v S^v \quad (3.11)$$

$$\frac{dE_i^v}{dt} = b_s m \beta^{hv} S^v \frac{I_i^h + \phi I_{ji}^h}{N^h} - r^v E_i^v - \mu_v E_i^v \quad (3.12)$$

$$\frac{dI_i^v}{dt} = r^v E_i^v + \omega I_i^e - \mu_v I_i^v \quad (3.13)$$

**<Host>**

$$\frac{dS^h}{dt} = \mu_{hb} N^h - S^h \left( \sum_{i=1}^4 b_i m \beta^{vh} \frac{I_i^v}{N^h} \right) - \mu_{hd} S^h \quad (3.14)$$

$$\frac{dI_i^h}{dt} = S^h b_i m \beta^{vh} \frac{I_i^v}{N^h} - \gamma^h I_i^h - \mu_{hd} I_i^h \quad (3.15)$$

$$\frac{dR_i^h}{dt} = \gamma^h I_i^h - R_i^h \left( \sum_{i \neq j} b_i m \beta^{vh} \frac{I_j^v}{N^h} \right) - \mu_{hd} R_i^h \quad (3.16)$$

$$\frac{dI_{ij}^h}{dt} = b_i m \beta^{vh} R_i^h \frac{I_j^v}{N^h} - \sigma^h I_{ij}^h - f I_{ij}^h - \mu_{hd} I_{ij}^h \quad (3.17)$$

$$\frac{dR}{dt} = \sigma^h \sum_{i \neq j} I_{ij}^h - \mu_{hd} R \quad (3.18)$$



### 3.3.3. Two strains model

According to annual trend of the influx of tourists infected by dengue fever into Korea, the tourists visited Southeast Asia, especially Philippine and Cambodia, comprise a large proportion of those infected by this disease. Although Korea government has yet to official investigation for serotypes of these people, each country trend of more prevalent serotypes has already well known and is shown in the **Table 3.2**.

Country	Major serotypes	Country	Major serotypes
Philippine	DEN3	Vietnam	DEN1, DEN2
Cambodia	DEN1, DEN2	Laos	DEN1, DEN2, DEN3
Thailand	DEN1, DEN4	Australia	DEN1, DEN2

**Table 3.2 Specific major serotypes by country**

On the whole, dengue fever seems to be mostly caused by DEN1 and DEN2 in Southeast Asia, so that patients having these two serotypes may be able to comprise a big proportion of domestic patients infected by dengue fever. Therefore, two strains (two serotypes) and secondary infection model reflecting the aspect of trend of outbreak of this disease can be formulated in order for more simplification. This model is described by ODE's describing the transition for primary infection with strain 1 and secondary infection with strain 2 as follows.

<Vector>

$$\frac{dS^e}{dt} = b_v \left( 1 - \sum_{i=1}^2 v \frac{I_i^v}{N^v} \right) - \omega S^e \quad (3.19)$$

$$\frac{dI_i^e}{dt} = b_v v \frac{I_i^v}{N^v} - \omega I_i^e \quad (3.20)$$

$$\frac{dS^v}{dt} = \omega S^e - S^v \left( \sum_{i=1, i \neq j}^2 b_s m \beta^{hv} \frac{I_i^h + \phi I_{ji}^h}{N^h} \right) - \mu_v S^v \quad (3.21)$$

$$\frac{dE_i^v}{dt} = b_s m \beta^{hv} S^v \frac{I_i^h + \phi I_{ji}^h}{N^h} - r^v E_i^v - \mu_v E_i^v \quad (3.22)$$

$$\frac{dI_i^v}{dt} = r^v E_i^v + \omega I_i^e - \mu_v I_i^v \quad (3.23)$$

<Host>

$$\frac{dS^h}{dt} = \mu_{hb}N^h - S^h \left( \sum_{i=1}^2 b_i m \beta^{vh} \frac{I_i^v}{N^h} \right) - \mu_{hd}S^h \quad (3.24)$$

$$\frac{dI_i^h}{dt} = S^h b_i m \beta^{vh} \frac{I_i^v}{N^h} - \gamma^h I_i^h - \mu_{hd}I_i^h \quad (3.25)$$

$$\frac{dR_i^h}{dt} = \gamma^h I_i^h - R_i^h \left( \sum_{i \neq j} b_i m \beta^{vh} \frac{I_j^v}{N^h} \right) - \mu_{hd}R_i^h \quad (3.26)$$

$$\frac{dI_{ij}^h}{dt} = b_i m \beta^{vh} R_i^h \frac{I_j^v}{N^h} - \sigma^h I_{ij}^h - f I_{ij}^h - \mu_{hd}I_{ij}^h \quad (3.27)$$

$$\frac{dR}{dt} = \sigma^h \sum_{i \neq j} I_{ij}^h - \mu_{hd}R \quad (3.28)$$

The notation of subscripts where  $i = 1$  and  $2$  means the primary infection and  $ji$ ,  $j = 3 - i$  is the secondary infection. This model divides the pre-adult mosquito population into two classes: susceptible ( $S^e$ ), infected with two strains, 1 and 2 ( $I^e$ ). Similarly, the adult mosquito population divided into five classes: susceptible ( $S^v$ ), exposed with strain one ( $E_1^v$ ) or strain two ( $E_2^v$ ) and the infected with strain one ( $I_1^v$ ) or two ( $I_2^v$ ). On the other hand, the human population is divided into eight classes: susceptible ( $S^h$ ), primarily infected with strain one ( $I_1^h$ ) or two ( $I_2^h$ ), recovered from the first infection with strain one ( $R_1^h$ ) or two ( $R_2^h$ ), secondarily infected with strain one when the primary infection is caused by strain two ( $I_{12}^h$ ), secondarily infected with strain two when having the primary infection caused by strain one ( $I_{21}^h$ ), and the recovered from the secondary infection ( $R$ ).

### 3.4. Parameters

#### 3.4.1 Parameters related to human

The human population size in Jeju Island of 550,044 individuals is sourced from the Statistic Korea, and the birth rate and death rate of this population are also estimated from the data on a yearly basis of Statistic Korea [32].

### 3.4.2. Constant parameters

**Table 3.3** shows the meanings of parameters, value and references for the comprehensive two models which are secondary infection model with four serotypes and two strains. The initial mosquito population is assumed 550,044 which is same as the initial population of human.

Symbol	Meaning	Value	References
$v$	Vertical infection rate	0.028	[8]
$\beta^{hv}$	Transmissible biting rate(h $\rightarrow$ v)	0.75	[9]
$\gamma^h$	First recovery rate for human	1/3	[9]
$\sigma^h$	Second recovery rate for human	1/7	[9]
$m$	The number of vectors per human	1	[8]
$b_s$	Biting rate per susceptible mosquito	0.25	[11]
$b_i$	Biting rate per infected mosquito	0.75	[11]
$f$	Fatality rate	0.000046	Estimated
$\mu_{hb}$	Birth rate of human	0.000025	Estimated
$\mu_{hd}$	Death rate of human	0.000015	Estimated
$N^v(0)$	Total number of mosquitoes	550044	Assumed
$N^h(0)$	Total number of human	550044	Calculation

**Table 3.3 Parameters of dengue fever models**

### 3.4.3. Climatic factors dependent parameters

Since the temperature has play important role determining the life cycle for mosquitoes, the parameters related to life for mosquitoes is estimated in terms of daily temperature. For example, define  $P$  be temperature dependent parameters and temperature  $x(t)$  be a function of time  $t$ , then  $P$  can be expressed by  $P = P(x(t))$ . The entomological parameters including the maturation rate, virus incubation rate, and death rate are estimated by using three fitting functions depending on only temperature [8,10]. These three temperature dependent parameters are expressed by a polynomial with degree  $n$ ,

$$P_n(x) = \sum_{k=0}^n a_k x^k$$

where  $x$  is the temperature and the coefficient  $a_k$  are obtained by using least squares method minimizing the sum of the squares of the residuals that are differences between fitted values and original values based on experimental data, in which the quantity  $b^2$ ,

$$b^2 = \sum_{j=1}^N \frac{P_n(x_j) - P_j}{\sigma_j}$$

is minimized, where  $N$  is total number of observation,  $P_j$  is observed value such as rate of maturation, virus incubation, and death for mosquito at temperature  $x_j$  and  $\sigma_j$  is the corresponding standard deviation of the random errors of  $P_j$ . When making fitting functions, degree of the polynomial  $n$  can be chosen appropriately. In this way, the parameters, maturation rate ( $\omega$ ), virus incubation rate ( $r^v$ ), transmission rate from mosquito to human ( $\beta^{vh}$ ) and death rate ( $\mu_v$ ) for mosquito, can be described as temperature fitted functions. These three functions are measured in range of  $10^\circ\text{C} < x < 35^\circ\text{C}$  because the empirical data for mosquito is obtained from Thailand and Taiwan.

### (1) Maturation rate

The maturation rate from pupae to adult mosquito is expressed by seventh order polynomial as follows.

$$\begin{aligned} \omega = & 0.1310 - 0.05723x + 0.01164x^2 - 0.001341x^3 + 0.00008723x^4 \\ & - 0.000003017x^5 + 0.00000005153x^6 + 0.000000342x^7 \end{aligned}$$

The range of this rate is from 0.00041/day to 0.1297/day can be showed [10]. The highest value of maturation rate 0.1297 occurs at  $26.5^\circ\text{C}$ , decreasing in the interval  $26.5^\circ\text{C} < x < 35^\circ\text{C}$  and increasing in the interval  $12^\circ\text{C} < x < 26.5^\circ\text{C}$ .

## (2) Virus incubation rate

The virus incubation rate per day is expressed by first order polynomial as follows [10].

$$r^v = 0.008x - 0.1393$$

The range of this rate is from -0.0593/day to 0.1407/day can be showed and the highest value 0.158/day happens at 35°C.

## (3) Transmission rate

In case of the transmission rate, it drops when temperature is high. Thus in order to capture this effect, the thermodynamic function is fitted to a set of empirical data. Thus the relationship between transmission rate and temperature is described by this function.

$$\beta^{vh} = 0.001044x(x - 12.286)x\sqrt{32.461 - x}$$

The value of this function increases for 12.4°C <  $x$  < 28°C and decreases rapidly when  $x$  > 28°C [20].

## (4) Death rate

The mortality rate per day is expressed by fourth degree polynomial as follows [10].

$$\mu_v = 0.8692 - 0.159x + 0.01116x^2 + 0.0003408x^3 + 0.000003809x^4$$

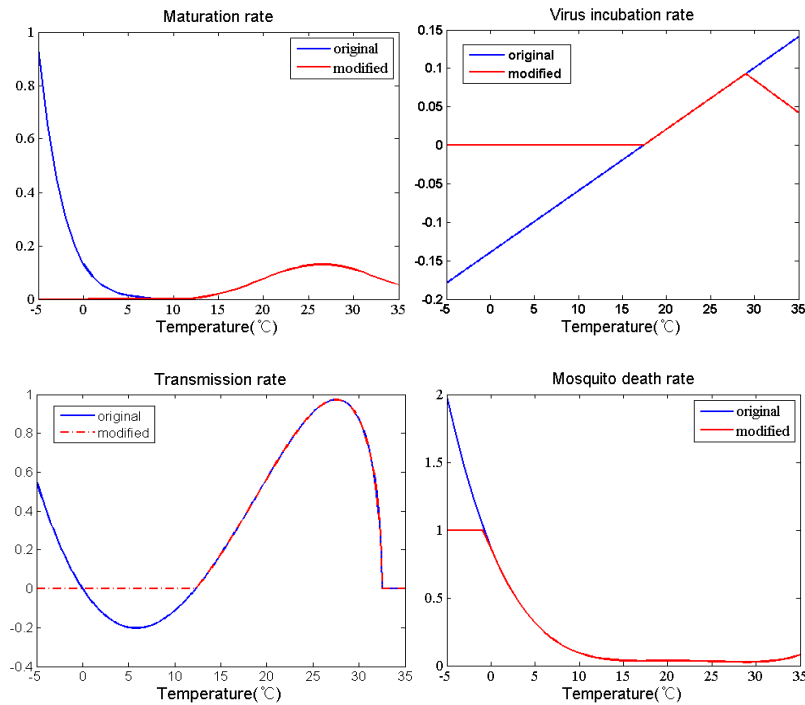
The range of this rate is from 0.026/day to 0.0925/day can be showed. The small death rate like a basin shape in the interval 15°C <  $x$  < 30°C is observed. The lowest death rate is 0.026/day at 29°C and it increases quickly when it get closer to the both boundaries ( $x$  < 14°C and  $x$  > 31°C).

## (5) Modification of parameters

These fitting equations for four parameters are derived from the database for temperature of subtropical country Taiwan and Thailand. The temperature of Taiwan ranges from 15°C to 35°C while the temperature of Thailand ranges from 19°C to 37°C. In this reason, there is no data for mosquito at

under 15°C. Thus, it is not suitable to estimate the parameters for the low temperature around the temperature range from -4 °C to 31 °C in Jeju Island.

As maximum temperature of Jeju Island is 31 °C, there is no problem for representation of each rate at temperature over 35°C. But it is necessary to revise about fitting functions at under 10°C including minimum temperature. So far, the researchers in Korea have yet to develop or record a database for relation of mosquito and temperature. Thus there is no experiment data about mosquito at the temperature in winter even under 10°C. So the fitting functions are revised, being fit to life cycle of mosquito according to temperature. The red lines and green line in the **Figure 3.6** show the values of modified parameters for fitting function in the interval  $-5^{\circ}\text{C} < x < 35^{\circ}\text{C}$ .



**Figure 3.5 Modified temperature dependent parameters:** Blue lines and red lines represent original parameters and modified parameters, respectively. In addition, the green line represents other modified incubation rate.

Maturation rate is nearly zero at about 10°C. But this rate suddenly increases at under 10°C. So at this interval, a value is set at zero. For the transmission rate, it has negative value and increases at under 12°C in original parameter. Thus at this interval, value is set at zero. As Virus incubation rate is linear function, it has value of minus at under 10°C and it is not reasonable to have high value over 29°C. Thus this function is revised as constant function so that value can be finally converged to zero at under 10°C and

set linear function with negative slop over 29°C. Death rate has value over one at under 0°C. So at the interval, value is set at one. The modified parameter function can be expressed as followed in **Table 3.4**.

Temperature dependent parameter	Modified function
Maturation rate	$\omega(x) = \begin{cases} 0, & x < 10 \\ \omega, & x \geq 10 \end{cases}$
Virus incubation rate	$r^v(x) = \begin{cases} 0 & x < 10 \\ r^v & 10 \leq x < 29 \\ \frac{-0.0084}{x-40} & x \geq 29 \end{cases}$
Transmission rate from mosquito to human	$\beta^{vh}(x) = \begin{cases} 0, & x < 12 \\ \beta^{vh}, & x \geq 12 \end{cases}$
Death rate in mosquito	$\mu_v(x) = \begin{cases} 0, & x < 0 \\ \mu_v, & x \geq 0 \end{cases}$

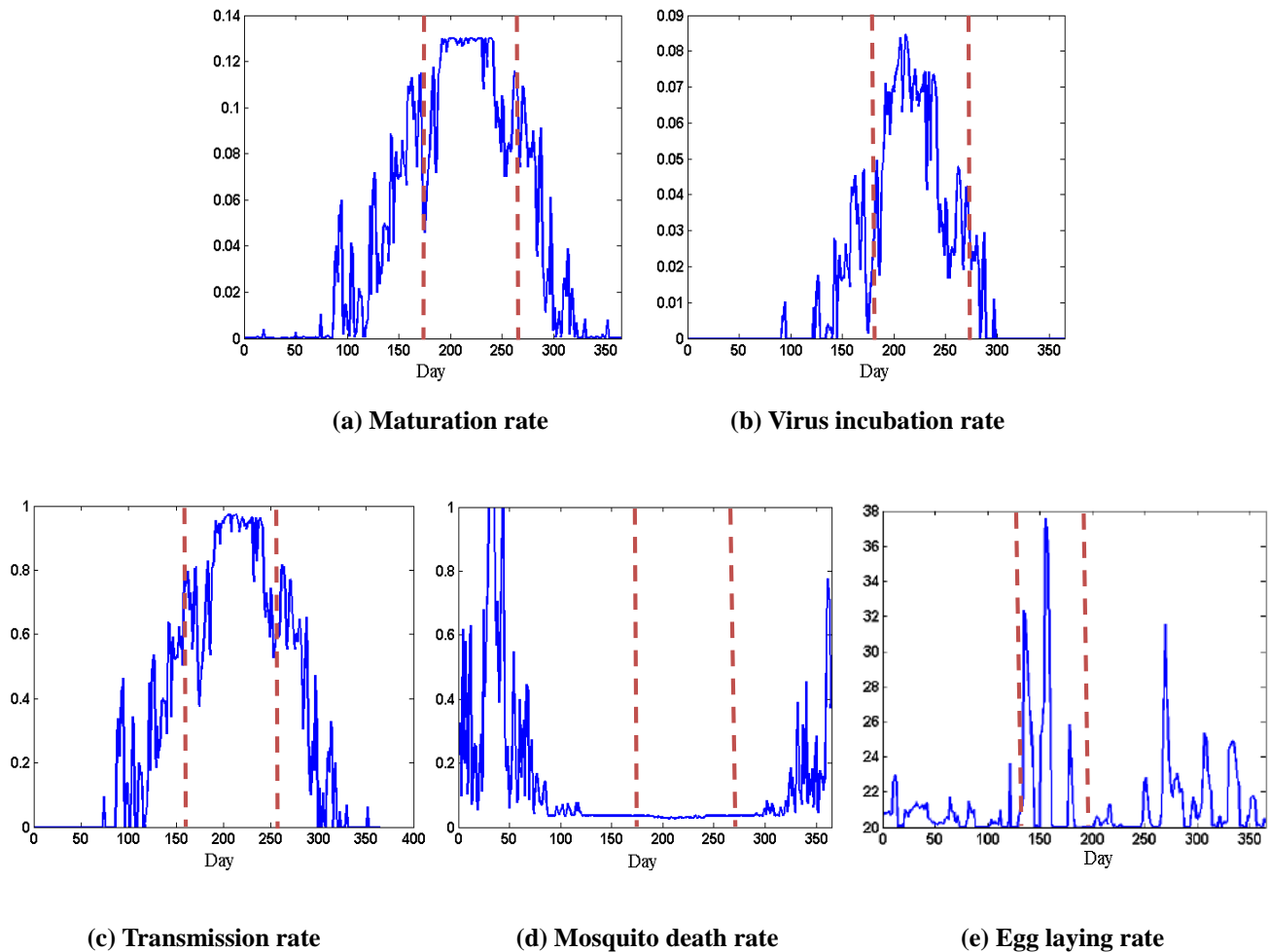
**Table 3.4 Modified functions for temperature dependent parameters**

#### (6) Egg laying rate

There is close correlation between climate and the number of laid eggs per day, thus egg laying rate can be estimated by using specific function depending on several climate factors such as temperature, relative humidity, precipitation, evaporation, and dew point [12,13]. The egg laying rate of mosquito  $b_v$  is expressed by using concept of moisture index, which is defined as difference of precipitation and evaporation (mm) over the preceding 7 days as follows.

- $b_v = b_0 + \frac{E \max}{1 + \exp(-\text{Moistureindex} + E_{\text{mean}}/E_{\text{var}})}$
- $\text{Moistureindex}(t) = \sum_{D=t-6}^t \text{precipitation}(D) - \text{evaporation}(D)$
- $\text{evaporation} = \frac{(700x - 0.006h/(100 - \text{latitude}))}{80 - x} + \frac{15(x - T_d)}{80 - x}$
- $T_d = \frac{237.7r(x, RH)}{17.271 - r(x, RH)}, \quad r(x, RH) = \frac{17.271x}{237.7 + x} + \ln \frac{RH}{100}$

The moisture index indicates the sum of subtraction of precipitation and evaporation for a week. Starting the rainy season, the moisture index can be bigger. The big moisture index make the denominator of egg laying rate also bigger. Eventually, the population of egg increase exponentially toward the peak in the rainy season. The parameter  $b_0$  represent the base egg laying rate which is the value of multiplying death rate of mosquito to the total number of mosquito population in order of conservation of total population. The value of latitude is obtained by calculating average latitude of two districts, Jeju-si and Seogwipo-si. Besides,  $T_d$  and RH are dew point and relative humidity, respectively. **Figure 3.7** shows aspect of five parameter functions for one year applied 2014 climate data.



**Figure 3.6** Five climatic factors dependent parameters related to mosquito for one year



**Figure 3.6 (a), (b), and (c)** show that maturation rate and virus incubation rate and transmission rate increase from June when temperature rises to October when temperature drops. The interval between red dot lines indicates these characteristics. These rates reflect that mosquitoes are mostly active from early summer to early fall. By contrast, mosquito death rate decreases during this period and is shown in **Figure 3.7 (d)**. The egg laying rate in **Figure 3.7 (e)** increases around June and July during the rainy season. These are supported by data for number of mosquito each month collected in ovitrap.

## 3.5. Results and Analysis

### 3.5.1. Results for Dengue Fever Model

Predicting the number of patients with infectious diseases is very hard and careful work. Considering the characteristic of infectious diseases, it is impossible to test them, and if the predicted number of patients is wrong, it could lead to waste of finance and lack of vaccines or medicines, which could produce more patients. In addition, it is necessary for simulating with only original parameters since the modified parameter made by reflecting life cycle of mosquito would be not able to be suitable for Korean climate. Therefore, it is rational to predict the future by setting up many models or one model under many assumptions, performing simulation, and comparing the results. Thus, in this study, simulation was performed by using two methods, one applying climate data of all the four seasons of Korea to the dengue model suggested above, and the other applying climate data of seasons excluding winter.

#### (1) Simulation with climate data for four seasons

By inputting climate data of the four seasons of Jeju Island, gained from 2014 to the present based on RCP 8.5 set under the assumption that global warming would progress rapidly, into each parameter function, daily parameter (maturation rate, virus incubation rate, transmission rate mosquito death rate, and egg laying rate) values were obtained. By applying these parameter values to each model and performing simulation for 50 years from 2014, the number of mosquitos, the number of patients, and the number of deceased people were predicted. Simulation was performed based on the assumption that infected mosquitos were living in Jeju Island and the first case of infection occurred in Jeju Island in January, 2014.

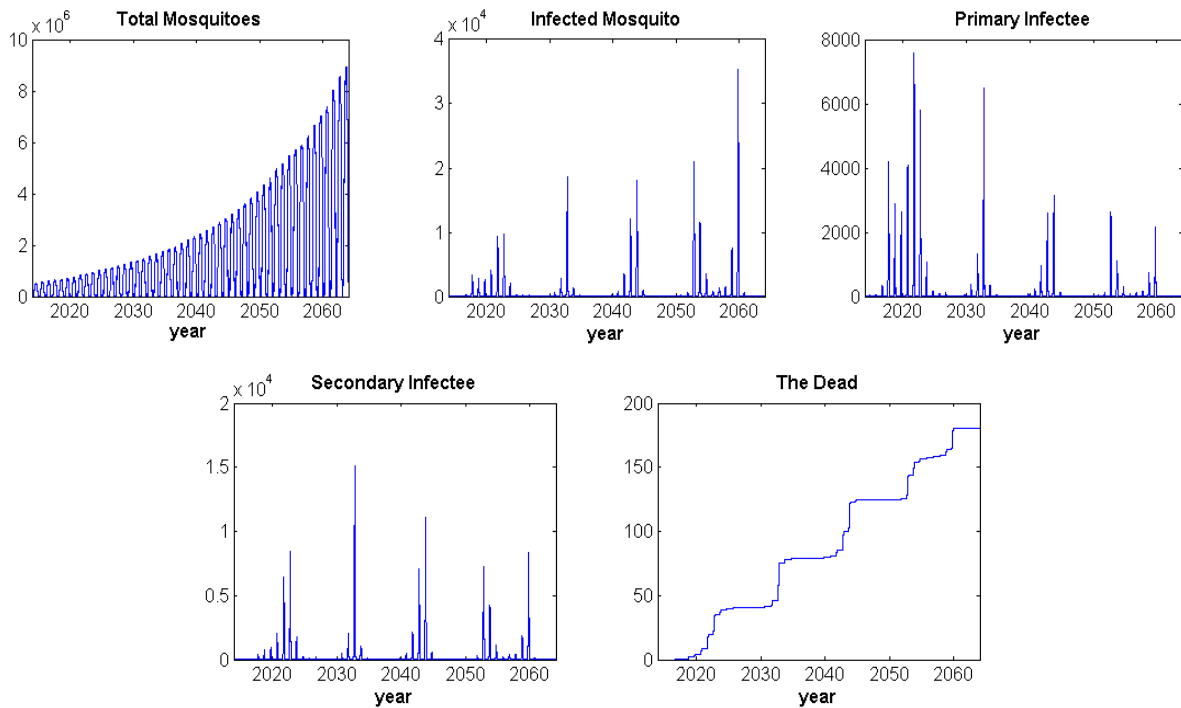
## 1) Simulation Method

The values shown in **Table 3.3** were applied to constant parameters for each model. Solutions for ODE expressing each model by using the ODE solver of Matlab were gained. The simulation period was 50 years, which is comparatively long, to predict the trend of the number of patients by season. And looking at the regions where dengue settled itself down, although the cause could not be determined, major outbreak took place at a certain period, and so it was tested whether that phenomenon was occurring in Korea by setting the simulation period long.

## 2) Results for Simulations

### ① Secondary infection model with four serotypes

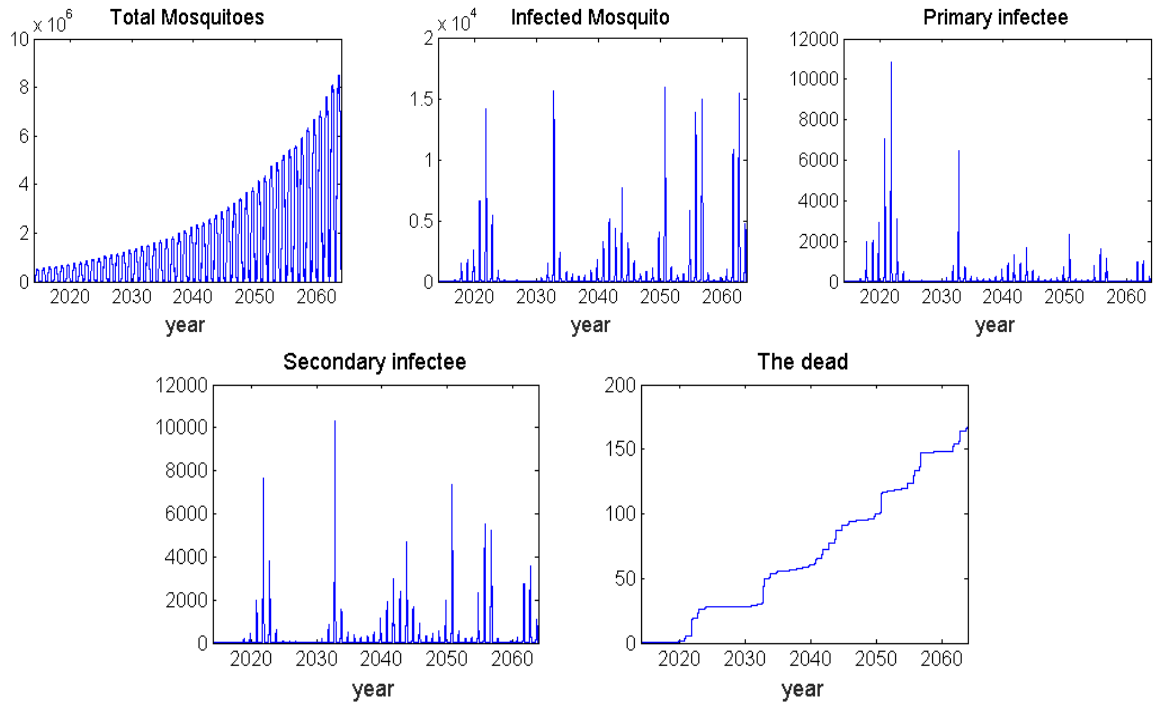
· Initial condition: The initial conditions of  $N^v(0)$ ,  $N^h(0)$ ,  $I^v(0)$  and  $I^h(0)$  are assumed to be 550044, 550044, 100 and 10 respectively.



**Figure 3.7 Results for secondary infection model with four serotypes**

## ② Secondary infection model with two strains

· Initial condition: The initial conditions of  $N^v(0)$ ,  $N^h(0)$ ,  $I^v(0)$  and  $I^h(0)$  are assumed to be 550044, 550044, 100 and 2 respectively.



**Figure 3.8 Results for secondary infection model with two strains**

## (2) Simulation with climate data expect winter

It could be hard for dengue to settle down and occur in the climate of Korea that has winter. Normally dengue mosquitos are active at over  $10^\circ\text{C}$  and go into hibernation in winter. Although Jeju Island is included in the subtropical region, because it has winter, mosquitos' activities could be limited, so another simulation method was devised. This method is to divide the four seasons into two parts and use only the climate data of June-October, excluding winter. In this method, the same assumption that the first case of infection occurred in Jeju Island was made, and it also applied the climate data reflecting RCP 8.5.

## 1) Simulation Method

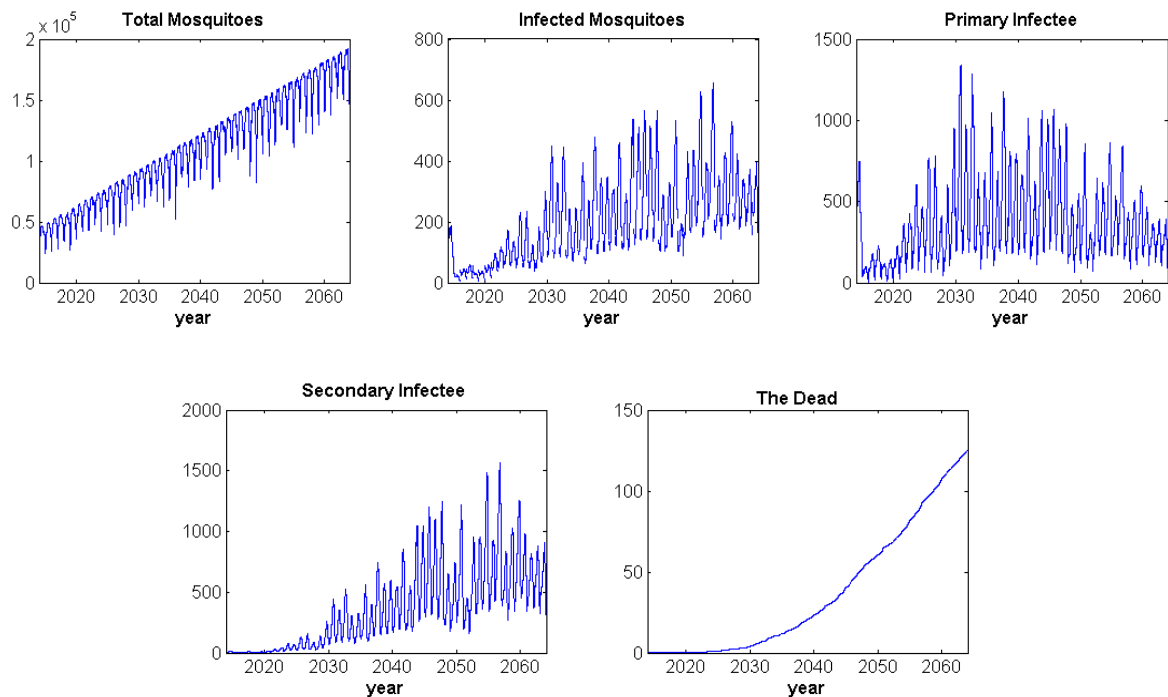
As there were no result values for winter, a new initial condition was applied every year. The annually applied initial condition is the ratio of each adult mosquito for total mosquitoes. The initial rate which total adult mosquito emerge from the larva considering seasonality can be expressed by

$$N^v(t) = N^v(0)(1 + A \sin\left(\frac{2\pi t}{T}\right))$$

where  $T$  is period and  $A$  is the strength of the seasonality in vectors in  $(0,1)$  depending on the values, 0.1, 0.5 and 0.9, which mean minimal seasonal forcing, moderate seasonal forcing, and high seasonal forcing, respectively. The minimal seasonality case ( $A = 0.1$ ) is relevant to tropical countries with weaker forcing without long dry spells. The large seasonal forcing ( $A = 0.9$ ) corresponds to tropical countries with low dry months. Thus, in this simulation, the moderate seasonal forcing is selected [18].

## 2) Results for Simulation

The initial conditions of  $N^v(0)$ ,  $N^h(0)$ ,  $I^v(0)$  and  $I^h(0)$  are assumed to be 20000, 550044, 100, and 2, respectively.

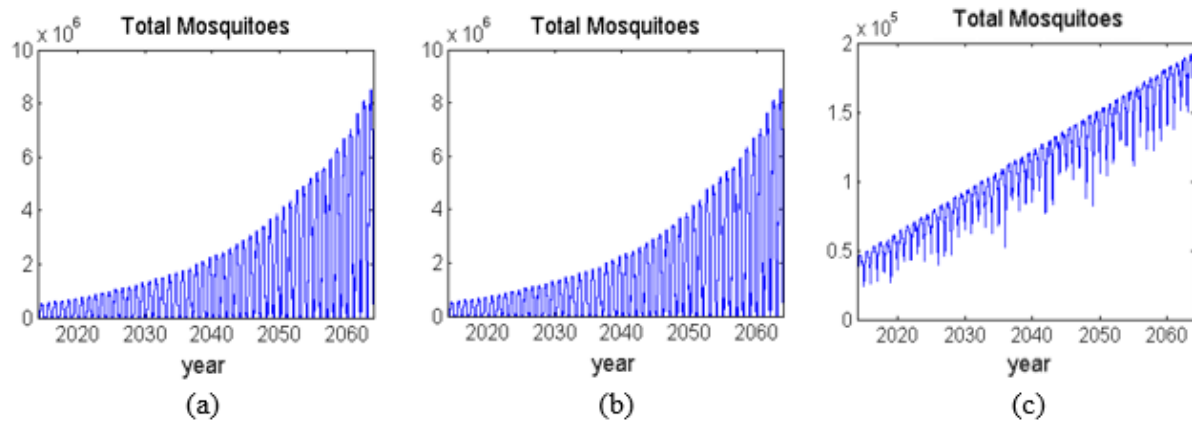


**Figure 3.9 Results for secondary infection model with four serotypes during summer**

### 3.5.2. Analysis for Results

In following **Figures 3.10 (a)** and **(b)** represent the results for simulations using four season data for secondary infection models with four serotypes and two strains, respectively. **Figure 3.10 (c)** represent the result for simulation adapting climate data excluding winter data with model for four serotypes.

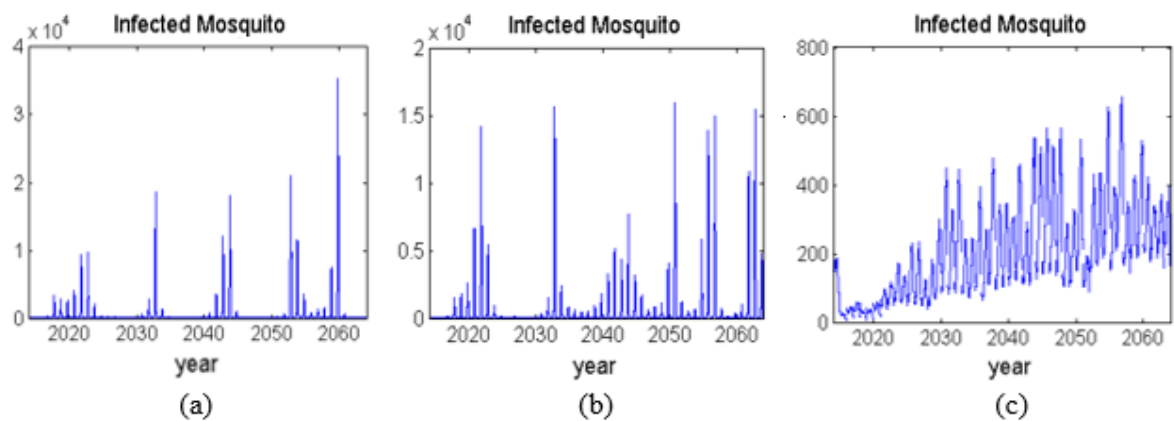
#### (1) The total number of mosquitoes



**Figure 3.10. Results for change of total mosquitoes**

As three types of results, total mosquitoes including non-infected and infected mosquitoes increase as time passes reflecting climate change in Jeju. The total mosquitoes in case of results by simulating based on climate data excluding winter shown in **Figure 3.10 (c)** is rapidly increase than other simulation results.

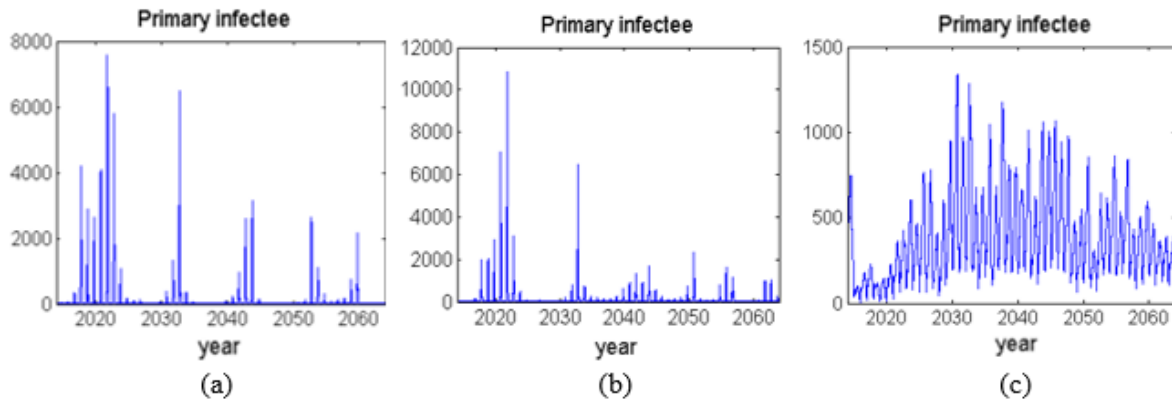
#### (2) The infected mosquitoes



**Figure 3.11. Results for spread of infected mosquitoes**

The infected mosquitoes tend to increase in case of secondary infection model with four serotypes shown in **Fig 3.11 (a)**. Since this model consider all serotypes, it takes relatively long time for being infected for mosquito. However, in case of secondary infection model with two strains represented in **Fig 3.11 (b)**, it has no this phenomenon due to only two strains. Thus the result of this model can be seen that infected mosquitoes do not increase as time passes but always have relatively large number of infected mosquitoes. In case of last result which is shown in **Fig 3.11 (c)** for using only summer data, the number of infected mosquitoes also tend to increase.

### (3) The primary infectee



**Figure 3.12. Results for spread of primary infectee**

These graphs in **Figure 3.12** are results for primary patients for 50years. As time passes, the number of primary patients decrease since they have immunity against certain one serotypes. In **Figure 3.12 (a)** and **(b)**, the number of primary patients for the two strains model tend to decrease rapidly than those for the four serotypes model since this model considers only two strains so that they have immunity a little faster. On the other hand, since model with four serotypes is built reflecting all serotypes from DEN1 to DEN4, the number of cases for infection is larger. In case of **Figure 3.12 (c)**, the number of primary patients also decrease as time passes.

(4) The secondary infectee

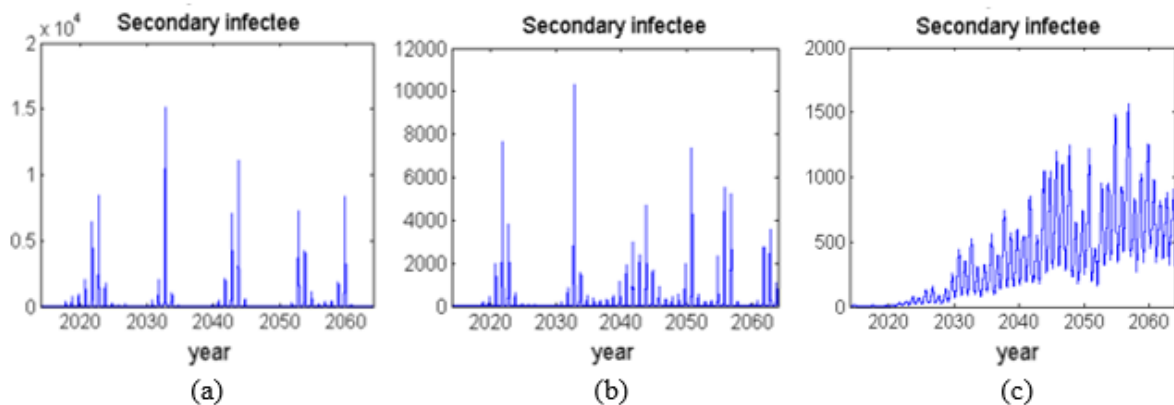


Figure 3.13. Results for spread of secondary infectee

After second major outbreaks which can be observed in **Figure 3.13 (a)** and **(b)**, the large number of patients at that time have recovered and have immunity so that small scale of outbreaks happen next time. This repeated phenomenon where the small size of outbreak happens again after major outbreak has been observed continuously. In addition, unlike the results using climate data excluding winter data, the result using four season data have repeated outbreak cycle. On the other hand, in the last results from simulating with summer data shown in **Figure 3.13 (c)**, there is no resting phase for occurrence of disease. This means that outbreak of dengue fever is determined by patterns of temperature, humidity and precipitation.

(5) The dead

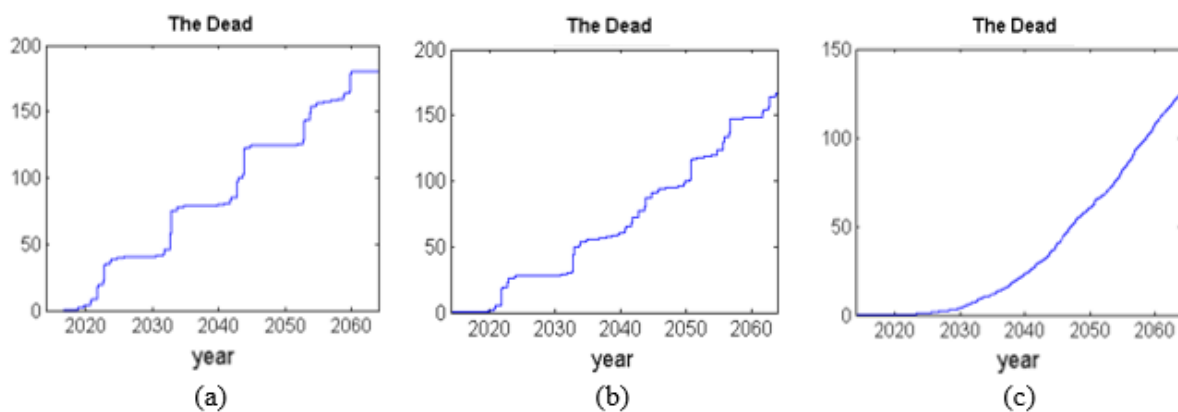


Figure 3.14. Results for occurrence for the dead

As these results for accumulated for the death toll, it is shown that the death from this disease occur continuously. Since the epidemic is limited to Jeju Island only, we should matter about hundreds of this fatalities caused by dengue fever seriously. Also, it is serious problem since this disease causes very extreme pain for patients.

## IV. Discussion and Future work

### 4.1. Limitations of Study

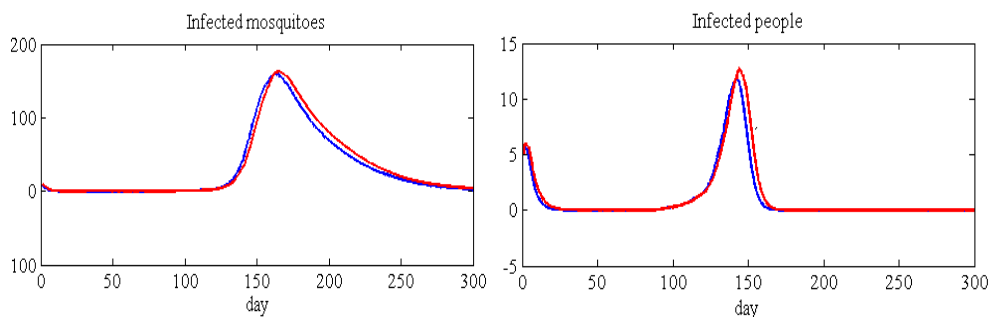
There are some limitations of this research. First, the models suggested in this study did not consider not only fourth infection including all serotypes but other factor such as temporary cross immunity which has great effect on symptom of disease. However, in order to solve this problem, extending the models by adding more compartments is not desirable to compute. And also, the parameters regarding mosquito did not reflect specific characteristic of life cycle of mosquito intimately related with climate factors since there is no detailed information or experimental data about dengue mosquito inhabiting in Korea. In this study, although there are only five climatic factor dependent parameters, other temperature dependent parameters related to mosquito can be expressed by mathematical equations. For example, the biting rate and probability of infection per one biting can be influenced by temperature. In case of biting rate, Scott(2000) suggested the function parameter as  $a = 0.03x + 0.66$  by using least square method based on weekly experimental data collected in Thailand. In addition, the transmission probability from infected human to susceptible mosquito can be described as  $\beta^{hv} = -0.9037 + 0.0729x$  which is studied by Lambrechts(2011). This study deals with only deterministic model for dengue fever. There are some assumptions in the deterministic model. The possibility that an individual who is part of a group will move to another group is all equal, therefore the differences of an individual's chances to be infected and the differences in his or her immune reaction cannot be considered; and since this model follows the law of mass action, then if the size of a group is big, the speed of movement from that group to another group is high. It is therefore useful when the size of the human group is relatively big. However, in cases where the size of the human group or initial condition is relatively small, the stochastic model is usually used. This model uses the concept of randomization to show the change of time or space, thus it can express the diversity in a real situation. In addition, the spatial structure (mosquito and human movement, distribution of oviposition site) and the mosquito behavior (biting, oviposition, mating) are not considered in this study. Thus, using the agent based model (ABM) taking account of a complexity of real world, the more detailed and realistic results can be obtained.



## 4.2. Stochastic Model for Dengue Fever

The deterministic methodology cannot reflect the stochastic characteristic of individuals within the compartment, for example, dengue occurs depending on the immune competence of people exposed to dengue virus. Due to interactions between this individual stochastic characteristic and various factors, it is hard to precisely predict the possibility of its outbreak. Due to the feature of stochastic approach for this disease in Korea, the target area of research, Jeju Island, has relatively small population size and the infection happens randomly with small initial conditions (small number of infected mosquito and host, small number of total population in restricted area). Generally, the stochastic model could give more precise results than the deterministic model through expressing the noise well. The deterministic model which is represented by ordinary differential equations is often appropriate when population size is large. Every time computing the models with the same initial conditions, the same outputs by various numerical methods in these models can be obtained. Otherwise, the stochastic model is often more suitable than the deterministic model when population size is relatively small. Every time running the model with the same initial conditions, the different outputs by using some methods which generate a random number can be occur.

The stochastic model for dengue fever based on direct Gillespie algorithm whose basic ideas are *i)* when does the next reaction happen *ii)* which reaction occurs after time interval  $\tau$  is computed. The chemical master equation is too high dimension to compute. Thus, Stochastic Simulation Algorithm (SSA) gets round this problem by simulating one sample time course from the chemical master equations rather than entire probability distribution. In this model, the reaction rates are replaced by propensity functions. The results, which are average and variance from the Gillespie algorithms for primary infection model are as in the following.



**Figure 4.1 Solutions for deterministic and stochastic primary infection model**

From sample numbers 10,000 with initial condition  $[N^v(0), N^h(0), I^v(0), I^h(0)] = [100, 100, 10, 5]$ , these results are obtained, and by comparing the results with those from the deterministic methodology, the differences of the solutions are found. In the graphs shown in **Fig 4.1**, the blue line is the solution obtained from the deterministic methodology and the red line is that gained from the stochastic methodology. The difference between the two solutions is the value gained by subtracting the stochastic solution  $y(t)$  from the deterministic solution  $x(t)$ , finding the absolute value, and then finding the maximum.

$$\text{Difference} = \max |x(t) - y(t)|$$

These values for difference are represented at **Table 4.1**. The relatively small population and initial conditions give us significant difference between two models. The difference can be reduced through repetitive realizations.

	Infected mosquito	Infected human
Difference	2.13837	2.54775

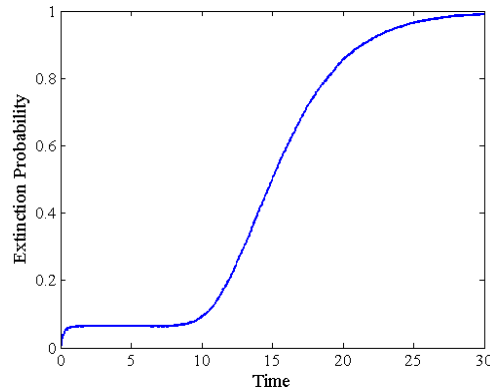
**Table 4.1 Difference of two types of solutions**

However, there are some limitations of this approach. First, the initial conditions for total mosquitoes or human are very small so that these results are not able to cover spread of dengue fever for entire regions of Jeju Island. In addition, the differences between solution of deterministic model and stochastic model are very small. This means that the stochastic characteristic of this disease are not reflected in this approach. In fact, if the difference is relatively large, it can be known that the stochastic model is proper to this disease.

### 4.3. Extinction Probability for Epidemic

In the perspective of stochastic approach, we can consider the extinction probability of disease. The disease can disappear due to stochastic fluctuation in contrast with the deterministic approach. In deterministic approach, the disease never goes extinct in a limited time since the number of patients decreases exponentially and goes zero only at infinity. The estimation for the extinction probability of disease can be obtained by probability generating function obtained by chemical master equation. From this function, expectation and variance for extinction can be calculated numerically. One way to

calculate the extinction probability is using the stochastic simulation algorithm. For example, in case of SIR model, the decreasing rate for infected people over time with initial condition  $S(0) = 49$ ,  $I(0) = 1$  and sample number 10000 is shown as follow.



**Figure 4.2 Probability of extinction for SIR model**

Using this method, the extinction probability for dengue fever considering climatic factors can be also estimated.

## V. Conclusion

Based on the fact that the first dengue fever patient was found in Jeju Island and on the premise of the process of climate change predicted by applying RCP 8.5, a climate change scenario without any carbon reduction policy adopted, this study proposed mathematical models for this disease and comparatively analyzed the simulation results. Carrying out research on the spread of epidemics is so sensitive and careful that we should establish several scenarios. Accordingly, this study proposed several mathematical models and carried out simulations with these models in various ways. There are three kinds of models suggested by this study, the primary infection model not considering serotypes, the secondary infection model considering 4 kinds of serotypes, and the secondary infection model considering only two kinds of serotypes likely to prevail in Korea. As dengue fever is a mosquito-borne epidemic mainly breaking out in subtropical and tropical regions, it may be difficult to get naturalized in Korea with relatively low annual temperature. In addition, since mosquito-related parameters are not made fit for the temperature of Korea, there may be some errors in the results of simulations including winter. Therefore, we carried out simulations in two ways, one including winter based on the scenario

of climate change, and the other using the climatic data only about June to October with winter excluded. In addition, a deterministic model is just used to focus on general aspects without concrete details, and since it cannot reflect various probabilistic elements of individuals composing the group, it is short of grounds to judge if the results are reliable. As dengue fever has not broken out or naturalized in Korea so far, it is not clear if the aspects of dengue-fever outbreak in Korea are similar to the results of this study. However, by examining the maximum starting point of dengue-fever patients, we can evaluate the simulation results of this prediction model suggested by this study. Besides, when we compare this model with actual cases of outbreak and have validity of the results of this study, we can apply it to the other areas where dengue fever is more likely to occur in Korea. In conclusion, as a result of applying this mathematical model developed by this study, dengue-fever patients were found most in summer, between July and August with high temperature and relatively abundant precipitation. Besides, it leads to a large-scaled outbreak at an interval of about 10 years, similar to the cases in other countries although the reason is not clear. Interestingly, it was found that as time goes by, there are more patients, which may indicate the naturalization of this disease in Korea. Further studies should be constantly conducted on other kinds of mathematical models to prevent the outbreak of dengue fever and establish and evaluate various national disaster strategies against pandemic diseases, and when the effect and cost of such a governmental counter-strategy are mathematically analyzed and examined, we can prevent and control such epidemics as dengue fever more efficiently.

## REFERENCES

- [1] G. T. Trewartha, L. H. Horn, *Modification of the Koppen Classification system in An Introduction to Climate*. 5th ed. (McGraw-Hill Inc, 1980)
- [2] Morita K, Dengue hemorrhagic fever, *Nippon Rinsho* **61(Suppl 2)**, 302-305 (2003)
- [3] T.S De Simone, Dengue virus surveillance: the co-circulation of DENV-1, DENV-2 and DENV-3 in the State of Rio de Janeiro, Brazil, *Trans R Soc Trop Med Hyg* **98**, 553-562 (2004)
- [4] F. Brauer , P. van den Driessche, J. Wu, *Mathematical Epidemiology*. (Springer, 2008)
- [5] W. O. Kermack, A. G. Mckendrick, A contribution to the mathematical theory of epidemics, *Proc R Soc Lond* **115(772)** , 700-721, 1927
- [6] D.Higham, Modeling and Simulating Chemical Reaction, *SIAM* **50**, 347-368
- [7] B.Adams, M, Boots, How important is vertical transmission in mosquitoes for the persistence of dengue? Insights from a mathematical model, *Epidemics* **2**, 1-10 (2010)
- [8] S.C.Chen, M. H. Hsieh, Modeling the transmission dynamics of dengue fever, Implications of temperature effects, *Science of the Total Environment* **431**, 385-391 (2012)
- [9] A.M. Greenberg et al., *Social Computing, Behavioral Cultural Modeling and Prediction*. (Springer, 2013)
- [10] H.M.Yang et al, Assessing the effects of temperature on the population of Aedes aegypti, the vector of dengue, *Epidemiol. Infect.* **137**, 1188-1202 (2009)
- [11] M. Derouci, A. Boutayeb, E. H. Twizwell, A model of dengue fever, *BioMedical Engineering OnLine*, 2-4 (2003)
- [12] H.Gong, A climate based mosquito population model, in *Proceedings of the World Congress on Engineering and Computer Science, San Francisco, Calif, USA, 2007 October*.
- [13] L. Xue et al., A hierarchical network approach for modeling Rift Valley fever epidemics with applications in North America, *PLoS ONE* **8(5)**, pp. e62049 (2013).
- [14] S.H.Lee et al., The Effects of Climate Change and Globalization on Mosquito Vectors: Evidence from Jeju Island, South Korea on the Potential for Asian Tiger Mosquito (Aedes albopictus) Influxes and Survival from Vietnam Rather Than Japan, *PLoS ONE* **8(7)**, pp. e68512 (2013)

- [15] B.W.Kooi, M.Aquiar, N. Stollenwerk, Analysis of asymptotic two-strain dengue model, *Mathematical Biosciences* **248**, 128-139, (2014)
- [16] M.H. Chung, Dengue fever, *Korean J Med* **77**, 165-170 (2009)
- [17] J. H. Park, Dengue fever in South Korea, 2006-2010, *Emerg Infect Dis* **18**, 1525-1527 (2012)
- [18] S.Polwiang, The seasonal reproduction number of dengue fever impacts of climate on transmission, *PeerJ PrePrints* 3, e1142 (2015)
- [19] Y. L. Hii, Climate and dengue fever: Early warning based on temperature and rainfall (Doctoral thesis), Umeå University (2013)
- [20] Lambrechts et al, Impact of daily temperature fluctuations on dengue virus transmission by *Aedes aegypti*, *PNAS* **108(18)**, 7460-7465 (2011)
- [21] E.Massad et al., Modeling the impact of global warming on vector-borne infections, *Physics of Life Reviews* **8(2)**, 169-199 (2011)
- [22] T.W. Scott et al, Longitudinal studies of *Aedes aegypti* (Diptera: Culicidae) in Thailand and Puerto Rico: Blood feeding frequency, *J Med Entomol* **37**, 89-101 (2000)
- [23] 기후변화 이해하기, 국립기상연구소(National Institute of Meteorological Research) (동진 문화사, 2009).
- [24] 장재연 외, 기후변화에 따른 건강분야 적응대책 수립방안 연구 최종보고서, 2009
- [25] 질병관리본부, 한국의 해외유입 뎅기열의 역학적 특성(Imported dengue cases in Korea), 1-5 (2008)
- [26] 질병관리본부, 2010년도 서태평양지역 국가들의 뎅기열 발생상황(Epidemiologic update on the dengue situation in the Western Pacific Region), 1-4 (2010)
- [27] 질병관리본부, 한국인의 뎅기열 감염실태와 역학적 상황, *CDMR* **14**, 1-7 (2003)
- [28] WHO, Dengue guidelines for diagnosis, treatment, prevention and control, <http://www.who.int/tdr/p/publications/documents/dengue-diagnosis.pdf> (2009)

[29] Korea Centers for Disease Control and Prevention, <http://www.cdc.go.kr/CDC/health>

[/CdcKrHealth0101.jsp?menuIds=HOME001-MNU1132-MNU1147-MNU0746-MNU0748&fid=753&cid=14224](http://www.cdc.go.kr/CDC/health/CdcKrHealth0101.jsp?menuIds=HOME001-MNU1132-MNU1147-MNU0746-MNU0748&fid=753&cid=14224)

[30] CDC, <http://www.cdc.gov/Dengue>

[31] Climate Change Information Center, <https://www.climate.go.kr:8005/index.html>

[32] Statistics Korea, 연령별(시도)추계인구, [www.kostat.go.kr](http://www.kostat.go.kr)

[33] Dengue Virus Net, [www.denguevirusnet.com](http://www.denguevirusnet.com)